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Promising Techniques in Sepsis After Cardiac Surgery

The purpose of this article is to give an up-to-date, comprehensive review on the utilisation of extracorporeal blood purification techniques and immunostimulation in septic patients after cardiac surgery.

Introduction

Sepsis is a potentially life-threatening state caused by an infection and an inadequate, dysregulated host immune response. In general, sepsis ranks in the top ten causes of death and is potentially harmful for the whole population of our planet (Lever and Mackenzie 2007; Martin et al. 2003). From the aspect of the intensive care unit, sepsis is one of leading causes of mortality despite the huge efforts and many different type of treatments (Mayr, Yende, and Angus 2014). Focusing on cardiac surgery, the prevalence of sepsis is low, after procedures situated between 0.39% and 2.5%. Nevertheless, the current life-expectancy of septic patients is poor, with mortality varying from 65% to 79% (Oliveira et al. 2010; Yaroustovsky et al. 2014).

A dysregulated interaction between the infection and the host immune system possibly lead to sepsis. During perioperative period of cardiac procedures, several additional, special factors are presented such as: (1) surgical trauma; (2) shear stress; (3) blood contacts with a huge artificial surface in cardiopulmonary bypass; (4) internal drainage system; (5) need for blood transfusion related to surgery; and (6) reperfusion after ischaemia. Reperfusion after ischaemia can lead to an increased endothelial permeability. In the gastrointestinal tract it possibly results in endotoxin or lipopolysaccharide (LPS) release. These factors together can provoke a dynamic systematic immune response (Paternoster and Guarracino 2016).

The pathophysiology and immunopathology of sepsis is still unclear. We were witnesses of several paradigm shifts during the last decade. Actually, we consider sepsis as a dynamic process with two different sides. Both immune hyperactivity and immune suppression are presented during the progression (van Ton et al. 2018). Immunomodulation is not a fresh idea in the treatment of sepsis. In order to develop a successful method in immunotherapy we should understand the progress of sepsis from the aspect of the immune system (Antonopoulou and Giamarellos-Bourboulis 2011; Cohen 2002).

Currently the diagnosis of sepsis is based on clinical signs. The biomarkers and molecular diagnostic tools are insufficient (Rhodes et al. 2017; Levy et al. 2018). Traditional prevention and treatment strategies have not changed significantly in the last decades and mortality is still alarmingly high.

During the last few years, several new approaches were studied. A large part of these approaches are based on immunomodulation, two of which are immunostimulation and extracorporeal blood purification techniques (Antonopoulou and Giamarellos-Bourboulis 2011).

The purpose of this article is to give an up-to-date, comprehensive review on the utilisation of extracorporeal blood purification techniques and immunostimulation in septic patients after cardiac surgery.

Immunopathophysiology of Sepsis After Cardiac Surgery

The actual concept of immunopathophysiology in sepsis is based on the idea of a dynamic parallel immune response; both pro- and anti-inflammatory processes are presented from the beginning (Annane et al. 2005). The innate immune system is responsible for the initial detection of potentially harmful factors, like microor-

ganisms and special inflammatory stress factors related to the perioperative period of cardiac surgery. Gram-negative and positive bacteria contain numerous structures (endotoxin, or lipopolysaccharide {LPS}, lipoprotein, peptidoglycans, peptidoglycan-associated lipoprotein, lipoteichoic acid, flagellin, fimbriae) that can lead to intense immune response. We call them pathogen-associated molecular patterns (PAMPs) (Kumar, Kawai, and Akira 2011). Surgical trauma and cardiopulmonary bypass cause a release of danger-associated molecular patterns (DAMPs). PAMPs and DAMPs are recognised by the pattern recognition receptors (PRRs) presented on dendritic cells, monocytes and macrophages. Toll-like receptors (TLRs) are one type of PRR. Binding of PAMPs and DAMPs to a PRR initiates the immune response of the host. The activation of different intracellular signalling cascades ends-up in a general activation of the innate immune system. The magnitude and type of primal response is influenced by many individual factors like age, type and amount of bacteria, comorbidities, genetic factors (Leentjens et al. 2013).

Proinflammation and antiinflammation walk hand-in-hand from the zero time point of the immune response. In the early phase, proinflammatic environment dominates. Mononuclear cells play an important role with the release of proinflammatory cytokines IL-1- IL-6, TNF-α. These classic proinflammatory mediators can lead to a fast and intense activation of the immune system called hyperinflammation (van Ton et al. 2018; Cohen 2002). Nevertheless, the immune system tries to maintain balance and launches a complex system of counter-regulatory mechanisms at the same time (Cohen 2002). These counter-regulatory attempts can end-up causing a phenomenon called "sepsis-induced immunoparalysis" (Venet et al. 2013). After the hyperinflammatory early phase, this immunosuppression possibly opens the field for secondary, opportunistic infections. Dominating molecules of this period are soluble TNF receptor antagonists, IL-1 receptor antagonists, IL-4, IL-10 and IL-13. Immunoparalysis is caused by impaired cytokine producing function of leukocytes, apoptosis of different type of immune cells, low absolute lymphocyte count and diminished expression of important cell surface antigens like HLA-DR on monocytes. The phenomenon of "sepsis-induced immunoparalysis" is supported by several studies and experiences. (1) Frequent occurrence or reactivation of less-virulent bacteria, viruses and fungi in the late phase of septic patients despite aggressive therapeutic efforts. (2) Mortality distribution of sepsis shows three peaks. Approximately a quarter of patients die in 4-5 days. From the remaining survivals one-third can bear with primal infection and restore immunocompetence - mortality of this group is 10%. The other two-third develop immunoparalysis and have a mortality rate of around 65% (Venet et al. 2013). (3) Studies with the application of antiinflammatory therapies show lack of positive effect on sepsis outcome (Leentjens et al. 2013).

> **"in order to develop a successful method in immunotherapy we should understand the progress of sepsis from the aspect of the immune system"**

Equilibrium may be the key in the immune response of sepsis. Immune system tries to maintain the homeostatic environment during sepsis via pro- and antiinflammatory processes. In case of an unbalanced, dysregulated and radical (in both directions) response, mortality becomes frightfully high. Of course, in reality it is more complicated and there are no clear borders between phases and extremities, like pro- and antiinflammation. Cytokines do not behave in a dichotomised manner; function and contribution to survival or death can depend on the context. A single cytokine possible act pleiotropically depending on the actual molecular microenvironment. The final effect of an inflammatory mediator is therefore diverse and highly depends on numerous different interactions (Denstaedt et al. 2018).

Treatment: New-Approaches Based on Immunomodulation

Infection source control, adequate antibiotic therapy and organ support are the three corner stones in the treatment of sepsis since the definition of sepsis was created (Zimmerman et al. 2004). Nowadays, the insufficiency of these treatments is clear and there is a need to improve clinical outcomes, especially in the late phase of sepsis. In the development and progression of sepsis, host immune response is an extremely important component. Complexity and heterogeneity of our immune system makes it clear that we will never be able to find a general answer for every septic patient; rather we should search for individual treatment modalities based on the clinical picture and immune-pathophyisiological background, patient-by-patient (Rello et al. 2017; Leligdowicz and Matthay 2019). Although these techniques are performing well in the early phase of sepsis, new adjuvant therapies are needed to prevent or treat the effects of the immunoparalytic phase of sepsis (Leentjens et al. 2013).

In our review we would like to add a detailed overview on two promising modalities of immunomodulation: (1) extracorporeal blood purification; (2) immunostimulation. Early days of sepsis is ruled by a hyperinflammatic state with DAMPs, PAMPs and proinflammatory cyto-

kines circulating in the body. Extracorporeal blood purification may represent a useful technique by removing these molecules from the circulation. In the late phase of sepsis immunoparalytic state appears in the majority of patients. To maintain equilibrium immunostimulation may offer a suitable opportunity (Antonopoulou and Giamarellos-Bourboulis 2011). Pro- and antiinflammatory responses and innate and adaptive immune systems may represent equal importance and become potential targets for immunomodulation strategies to improve outcome (Delano and Ward 2016).

Based on the nature of the immunopathophysiology of sepsis and our therapeutic goals with immunomodulation to maintain immune equilibrium, we must recognise the possible intervention points early and precisely. Appropriate immunomonitoring seems unavoidable and has a huge importance to recognise the patients with an overturned immune system as soon as possible (Venet et al. 2013; Denstaedt et al. 2018). Unfortunately, a detailed description of these methods is beyond the scope of this present review.

Extracorporeal Blood Purification

Extracorporeal blood purification techniques have a history of 15 years in the treatment of critically ill patients. A serious inflammatory host response includes an immune hyperactivity and an excessive release of proinflammatory cytokines. It leads to organ damage, dysfunction and immune-paralysis which possibly end up, in adverse outcomes, with death. This phenomenon summoned the original idea of blood purification (Honoré and Matson 2004; Di Carlo and Alexander 2005; Rimmele and Kellum 2011). Removing or reducing the blood concentrations of inflammatory mediators, bacterial toxins (endotoxin, LPS) and tissue degradation products from the systemic circulation with a special device can provide beneficial effects (preventing multi-organ dysfunction and immune- paralysis). Through that period numerous different strategies were studied, such as haemofiltration, haemoadsorption, plasmapheresis etc. Studies report promising results; these approaches can significantly reduce the blood concentration of the targeted molecules and are well tolerated by patients (Born et al. 2017). However, the details (appropriate technique, patient selection, timing, duration etc.) and the effect on clinical endpoints (mortality, organ dysfunction) is unclear yet. In technical aspects we can distinguish three different types: (1) haemofiltration (high volume haemofiltration, very high volume haemofiltration, high cut-off membranes); (2) adsorption (Toraymyxin, EMiC2, Cytosorb, Oxiris, LPS adsorber and HA 330) (3) coupled plasma filtration adsorption (Ankawi et al. n.d.). These methodologies can be applied with appropriate renal replacement therapy devices as an adjuvant treatment or alone.

> **in the late phase of sepsis immunoparalytic state appears in the majority of patients**

Haemofiltration techniques are feasible and safe in the setting of sepsis. Probably they can improve haemodynamics. Nevertheless, the effect on mortality is unclear, despite promising early results. Adsorption strategies are well-tolerated and feasible in septic patients. Currently we lack robust evidence, however, a positive trend seems to be emerging with improved haemodynamics and decreased mortality. Coupled plasma filtration adsorption technique is complex, expensive and associated with multiple technical issues. Evidence suggests feasibility and ineffectiveness in clinical endpoints; to date the power of these trials are limited (Ankawi et al. n.d.). Overall, the magnitude of currently available evidence on these techniques are admittedly insufficient, further efforts are warranted to ascertain the beneficial effects.

Utilisation of Cytosorb is one of the most promising and actual field among extracorporeal blood purification techniques. Cytosorb treatment is already tested in different clinical settings. It seems significantly effective in reducing toxic molecules and may improve the clinical outcome (Calabrò et al. 2019; Nemeth et al. 2018). Three small RCTs in the setting of sepsis and septic shock showed significant reduction in IL-6 concentration and significant reduction in vasopressor need, but no significant difference in mortality (D Schädler et al. 2013; Dirk Schädler et al. 2017; Hawchar et al. 2019). Each study confirms the safety and feasibility of the method. The international registry on the use of Cytosorb with 135 septic patients reported an improvement in observed mortality compared to predicted mortality, however, the number of patients is still a huge barrier to make further conclusions (Born et al. 2017). Several smaller studies and case series also support the above mentioned beneficial trends in haemodynamics and survival (Friesecke et al. 2017; Kogelmann et al. 2017).

Immunostimulation

Immune response during the dynamic process of sepsis is complex and contextual, however, a robust body of evidence remark a relationship between the presence of sepsis-induced immunoparalysis and poor clinical outcomes (Denstaedt et al. 2018). Numerous pre-clinical and clinical study report that sepsis leads to an overall state of immune depression with T cell dysfunction, impaired antigen presenting cell functions (monocytes, macrophages, dendritic cells) (Williams et al. 1998; Fan et al. 2015). Approximately 70% of sepsis related mortality occurs in later phase

of progression, which is defined by the persisting primary infection and sepsis related immune suppression with serious secondary opportunistic, nosocomial infections (Otto et al. 2011). Therefore, the development of novel strategies to augment host immunity may represent useful tools in the treatment of sepsis. Several diverse agents are already tested, although our current knowledge is based on animal studies and few clinical studies (Patil et al. 2016).

Granulocyte colony stimulating factor (G-CSF) and Granulocyte-macrophage colony stimulating factor (GM-CSF) are cytokines, which can stimulate stem cells to produce macrophages, monocytes and neutrophils and also improve release and function. Several clinical studies reported promising results and also a meta-analysis of 12 clinical studies demonstrated a significantly reduced rate of secondary infections (Francisco-Cruz et al. 2014; Bo et al. 2011). G-CSF and/or GM-CSF potentially become useful in the eradication and prevention of infections (Delano and Ward 2016).

Interferon gamma (IFN-γ) is one of the key cytokines responsible for appropriate monocyte and macrophage function, which are important factors in microbial elimination. Recombinant IFN-γ therapy increase antigen presenting capacity and proinflammatory cytokine production in septic patient without therapy related adverse outcomes (van Ton et al. 2018). Beneficial effects are already proofed in different patient population with an impaired immune system (Dries et al. 1994). Careful utilisation of IFN-γ may provide a therapeutic intervention for septic patients.

IL-7 is one of the most important cytokines in T cell production and function and also inhibits lymphocyte apoptosis. Therefore, recombinant IL-7 might offer benefit in lymphopenic septic patients (Rezoagli et al. 2019). A recent phase IIb randomised controlled trial results are suggesting recombinant IL-7 is a safe and feasibly option to enhance the adaptive immune response in septic patients (Francois et al. 2018).

Immunoglobulins (Ig)

Immunoglobulins are produced and secreted by B-cells that are activated and propagated by the T cells. Igs are constituted by heavy (H) and light (L) chains and Ig isotypes are classified into IgG, IgA, IgM, IgD and IgE (Shankar-Hari et al. 2011). Both H and L chains are divided into one variable and one constant domain (Shankar-Hari et al. 2011). It is well known that Igs are the major effectors of the humoral immune response, nevertheless, the exact mode of action of Ig remains largely unexplored. On one hand, Igs have the role to protect the host from infection, but on the other hand they may play a dual antithetical role as pro-inflammatory or anti-inflammatory agents (Berlot et al. n.d.).

Immunoglobulins are mandatory elements of adequate pathogen recognition and clearance. They inhibit the transcription of immune mediator genes and have anti- apoptotic effect (Vincent and Mongkolpun 2019). Sepsis is associated with decreased circulating immunoglobulin levels (especially IgG and IgM) levels (Taccone et al. 2009; Venet et al. 2011). Even if the mechanisms of action are still not fully elucidated, basic immunology and more recent studies indicate that endogenous Ig as well as the possible Ig supplementation may play a fundamental role in the host inflammatory-immune response to infection. Not only Ig (particularly IgM) can facilitate the rapid pathogen and toxin clearance in the early phases of infection and modulate the excessive pro-inflammatory host response, but they may be also beneficial in the late phases of sepsis characterised by a profound depression of innate and adaptive immunity. Ig exert a direct anti-apoptotic effect on lymphocytes and facilitate the clearance of apoptotic cells by an IgM-mediated mechanism that may counteract sepsis-induced immune- dysfunction (Schwab and Nimmerjahn 2013).

A recent meta-analysis with trial sequential analysis (TSA) for the primary and secondary outcomes which included 15 RCTs, involving 712 patients, and four cohort studies, involving 818 patients, assessed the use of intravenous (IV) IgGM preparations in adults with sepsis. IV IgGM administration significantly reduced mortality rates, with an RR of 0.60 (95% CI 0.52–0.69). Subgroup analysis showed that these results were generally consistent, regardless of duration of treatment, daily dose, total dose, variety of disease severity scores, follow-up duration, study design and year of publication. However, use of IV IgGM shortens mechanical ventilation days but not length of intensive care until stay or length of hospital stay (Cui et al. 2019).

Therefore, the possibility of direct immunoglobulin supplementation seems to be a worthwhile attempt. On one hand, results of recent studies are inconsistent (Kakoullis et al. 2018; Welte et al. 2018). On the other hand, the body of evidence is still insufficient for making further conclusions.

Immunostimulation in sepsis is currently in the scope of high scientific interest with great efforts to develop further progress. Numerous ongoing projects are investigating for other possible therapeutic interventions (IL-3, IL-15, anti-PD-1 antibody, anti-PD-L1-antibody, anti-BTLA antibody, anti-CTLA4 antibody, Flt3 ligand, CAR T cell therapy) (Patil, Bohannon, and Sherwood 2016).

Conclusion

Sepsis already has a long history, the intention to cure septic patients probably far older than the first definition of sepsis. During the last decade the potential outcome of sepsis in different patient population has not improved significantly.

Nevertheless, studies revealed the complexity and diversity of the immune response in septic patient. Numerous individual factors are recognised, which can lead to different progression patient-by-patient. Different types of immunomodulation techniques have a great prospect. However, the potentially beneficial utilisation may require a bigger and stronger body of evidence and an individualised approach for every single septic patient. A more accurate understanding of the immunopathophysiology of sepsis can lead to new approaches in treatment to improve the currently poor outcome.

Conflict of Interest

None. ■

Key Points

- Sepsis ranks in the top ten causes of death.
- The current life-expectancy of septic patients is poor and mortality varies from 65% to 79%
- Pathophysiology and immunopathology of sepsis is still unclear.
- Different types of immunomodulation techniques have a great prospect. However, their utilisation may require a bigger and stronger body of evidence and an individualised approach for every single septic patient.
- Understanding the immunopathophysiology of sepsis can lead to new approaches in treatment and improved patient outcomes.

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